

REMARKS/ARGUMENTS**I. Status of the Claims**

Claims 1-8, 10, 11, 47-51, 61 and 65 are pending.

The Patent Office objected to the form of claim 8.

Claims 1-8, 10, 11, 47-51, 61 and 65 stand rejected under 35 U.S.C. §112, second paragraph, as indefinite.

Claims 1-8, 10, 11, 47-51, 61 and 65 stand rejected under 35 U.S.C. §112, first paragraph, enablement.

Claims 1-8, 10, 11, 47-51, 61 and 65 stand rejected under 35 U.S.C. §112, first paragraph, written description.

Claims 2, 4-5, 7 and 11 stand rejected under 35 U.S.C. §102(b) as anticipated by, or in the alternative obvious over, Mahairas et al., Locus AQ495547.

Finally, the Patent Office issued a provisional double patenting rejection of claims 1-8, 10, 11, 47-51, 61 and 65 over copending Application No. 10/449,140.

Claims 1, 2, 3, 8 and 10 have been amended in the present Response. Support for the amendments to claims 1, 2 and 3 can be found throughout the specification as filed, for example on page 145, lines 23-28. Support for the amendment to claim 10 is found in the language of claim 10 itself.

II. Response to the Objection to Claim 8

The Patent Office objected to claim 8 as depending from a multiple dependent claim without employing alternative language.

Applicants submit that the amendment to claim 8 overcomes the Patent Office's objection. Accordingly, applicants respectfully submit that the objection to claim 8 be reconsidered and withdrawn.

III. Response to the Rejection of Claims 1-8, 10, 11, 47-51, 61 and 65 Under 35 U.S.C.§112, Second Paragraph

The Patent Office rejected claims 1-8, 10, 11, 47-51, 61 and 65 under 35 U.S.C. §112, second paragraph, as indefinite. Applicants traverse the rejections and submit the following comments, addressing each rejection in turn.

A.

The Patent Office rejected claims 1-3 under 35 U.S.C. §112, second paragraph, as indefinite. It is the Patent Office's position that although applicants included the recitation of a wash step in claims 1-3, the claims remain indefinite because "the person of ordinary skill in the art would have known that such a wash step was inherent to the process, and because no specific wash conditions are stated." *Office Action*, page 2.

Applicants submit that those of ordinary skill in the art would be fully aware of suitable high stringency wash conditions and that the claims are definite as currently pending. Nevertheless, in an effort to advance prosecution applicants have added a recitation of specific wash steps to claims 1, 2 and 3. Applicants submit that this explicit recitation in the claims overcomes the Patent Office's rejection. Accordingly, applicants respectfully request that the rejection of claim 65 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

B.

The Patent Office rejected claim 3 as "indefinite at part (b), which states that the claimed nucleic acid encodes 'a mature form', but allows insertions at the amino terminus of the polypeptide." *Office Action*, page 2. The Patent Office continues, "part (e) of the claim states that the encoded protein is 'a mature' form but allows N- and C- terminal deletions, which conflicts with the art-accepted meaning of 'mature' form of a protein." *Office Action*, pages 2-3.

Applicants have amended the subparts of claim 3 to recite the feature that the claimed alterations in the mature form are located in the region extending from residue 25 to the C-terminus of SEQ ID NO:1.

By this amendment to claim 3, applicants intend to capture minimal modifications, deletions and insertions into the mature form of the polypeptide. Applicants do not see anything incongruous in reciting a mature polypeptide and claiming deletions and truncations of that sequence. A mature form of a polypeptide is a sequence that has been processed, for example to remove a signal sequence. The processed, i.e., mature, form of the polypeptide can be further modified to provide a minimally different sequence yet still exhibit the recited activity. Examples of such minimal modifications can include additions, deletions and point mutations. To the extent these types of modifications generate a sequence with the recited activity, such sequences fall within the scope of applicants' invention. Applicants submit that one of ordinary skill in the art would recognize that the claim encompasses modifications to the mature form of the polypeptide and that the metes and bounds of the claim are definite.

Applicants submit that the amendments to claim 3 overcome the Patent Office's rejection. Accordingly, applicants respectfully request that the rejection of claim 3 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

C.

The Patent Office rejected claim 10 as indefinite "because it is not clear whether applicants intend that the 'native' promoter DNA is absent or not." *Office Action*, page 3.

Applicants disagree with the Patent Office's interpretation of the claim and believe the claim is definite as written. Nevertheless, in an effort to advance prosecution, applicants have amended claim 10 to recite that the nucleic acid molecule comprises promoter DNA operatively linked to the DNA encoding the polypeptide, wherein the promoter DNA is not the native promoter DNA.

Applicants submit that the amendments to claim 10 overcome the Patent Office's rejection. Accordingly, applicants respectfully request that the rejection of claim 10 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

D.

The Patent Office rejected claim 65 as indefinite because it is the Patent Office's position that claim 65 is "lacking sufficient method steps or elements. There is nothing recited in the claim or claim 4, from which it now depends, that would allow production of an $\alpha 2$ subunit." *Office Action*, page 3.

Applicants submit claim 65 is definite as written. Claim 65 recites culturing the host cell of claim 5 under suitable conditions to express the $\alpha 2/\beta 10$ heterodimer, and optionally isolating the $\alpha 2/\beta 10$ heterodimer from the solution. Methods of expressing recombinant proteins are well-known and can be employed in the claimed method to produce an $\alpha 2$ polypeptide. As the metes and bounds of the claim would be known to one of ordinary skill in the art, applicants do not need to provide anything further. Given the level of skill in the art and the developed nature of the relevant field, applicants submit that the claim as written provides clear boundaries to others as to what constitutes infringement of the claim, which is the purpose of 35 U.S.C. §112, second paragraph. To the extent additional steps *could* be provided, applicants are not obligated to do so for purposes of satisfying 35 U.S.C. §112, second paragraph. "The examiner's focus during examination of claims for compliance with the requirement for definiteness of 35 U.S.C. §112, second paragraph, is whether the claim meets the threshold requirements of clarity and precision, *not whether more suitable language or modes of expression are available.*" MPEP §2173.02 (emphasis added). Only a reasonable degree of particularity and distinctness is required. *Id.*

Applicants submit claim 65 is definite as written and respectfully request that the rejection of claim 65 under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

E.

The Patent Office rejected all claims as depending from an indefinite claim. Applicants submit that, in view of the amendments and arguments presented herein, all claims are definite. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §112, second paragraph, be reconsidered and withdrawn.

IV. Response to the Rejection of Claims 1-8, 10, 11, 47-51, 61 and 65 Under 35 U.S.C.§112, First Paragraph, Enablement

The Patent Office rejected claims 8, 10, 11, 47-51, 61 and 65 Under 35 U.S.C. §112, First Paragraph, as not enabled. It is the Patent Office's position that "[w]hile an $\alpha 2/\beta 10$ heterodimer binds to TSH receptors, it remains that no activity has been shown to result from that; there is no evidence of record that the claimed subunit 'is capable of regulating thyroidal function or promoting thyroid differentiation or proliferation. The newly discovered subunit may or may not stimulate the TSH receptor. It might just as well prevent signaling through that receptor. In the absence of any information as to what the biological activity is, the specification merely provides an invitation to experiment to determine what the $\alpha 2/\beta 10$ heterodimer does, and then develop methods of using it based upon those observations.'" *Office Action*, pages 3-4. Applicants traverse the rejection and submit the following comments.

While admitting that the heterodimer binds to TSH receptors, the Patent Office has nonetheless rejected the claims, apparently on the basis that applicants allegedly do not provide information on whether the binding event stimulates or inhibits signaling through TSH receptors. Applicants respectfully submit that the Patent Office has adopted an inappropriate standard in its analysis. In order to satisfy 35 U.S.C. §112, first paragraph, applicants need only provide enough guidance for one of ordinary skill in the art to make and use the *claimed* invention and applicants have done this. As the courts have said, in order "to comply with 35 U.S.C. 112, first paragraph, it is not necessary to 'enable one of ordinary skill in the art to make and use a perfected, commercially viable embodiment absent a claim limitation to that effect.'" MPEP § 2164, quoting *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1338 (Fed. Cir. 2003).

Applicants further note that applicants are not claiming a particular method of regulating, e.g., stimulating or inhibiting, thyroid function or promoting thyroid differentiation or proliferation. In this regard, applicants direct attention to Example 6, wherein applicants describe the creation of transgenics expressing $\alpha 2$ alone, $\beta 10$ alone and $\alpha 2$ and $\beta 10$ together. The $\alpha 2/\beta 10$ overexpressor animals showed bilaterally enlarged thyroid glands with multiple follicular papillary adenomas, while the $\alpha 2$ alone and $\beta 10$ alone overexpressors did not. Contrary to the Patent Office's position, the specification does describe what the $\alpha 2/\beta 10$ heterodimer does: it is capable of regulating thyroidal function or promoting thyroid differentiation or proliferation, as evidenced by the data on the transgenic animals presented in Example 6 shows. Applicants have met their obligation under 35 U.S.C. §112, second paragraph, enablement. To the extent the Patent Office is apparently requiring detailed data regarding the mechanism by which the phenotype is generated by a binding event involving TSH receptors and the heterodimer, applicants submit that there is no such duty, and requiring a detailed explanation is incompatible with the relevant case law. As the Federal Circuit stated, "it not a requirement of patentability that an inventor correctly set forth, or even know, how or why the invention works." *Newman v. Quigg*, 877 F.2d 1575, 1581 (Fed. Cir. 1989).

Applicants also note that, although the specification explicitly defines the meaning of the terms " $\beta 10$ polypeptide allelic variant" (page 21, lines 9-12) and " $\beta 10$ polypeptide splice variant" (page 23, lines 1-5), they have deleted element (b) of claim 2, which recites allelic and splice variants.

Applicants' statutory obligation is to enable one of ordinary skill in the art to make and use the invention as claimed, and applicants have done this. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §112, first paragraph enablement, be reconsidered and withdrawn.

V. Response to the Rejection of Claims 1-8, 10, 11, 47-51, 61 and 65 Under 35 U.S.C. §112, First Paragraph, Written Description

The Patent Office rejected claims 1-8, 10, 11, 47-51, 61 and 65 under 35 U.S.C. §112, first paragraph, as not complying with the written description requirement. The Patent Office refers to the Office Action mailed November 21, 2002 for the basis of the rejection but does not offer anything further. Applicants traverse the rejection and submit the following comments.

Referring to the Office Action of November 21, 2002, in that Action the Patent Office apparently based its rejection on the observation that the rejected claims recited variants, splice variants, orthologs, naturally occurring variants and sequences that hybridize under stringent conditions. In an effort to advance prosecution, but without agreeing with or acquiescing to the Patent Office's position, applicants have deleted these claim elements.

With respect to the hybridization elements of the rejected claims, applicants note that the Federal Circuit has indicated that a claim that recites a genus of nucleotide sequences based on their hybridization properties "may be adequately described if [the claimed nucleic acid molecules] hybridize under highly stringent conditions to known sequences because such conditions dictate that all species within the genus will be structurally similar." *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1327 (Fed. Cir. 2002). Applicant also notes that the claims 1-3 have been amended to recite hybridization at 42°C in a buffer comprising 0.015M sodium chloride, 0.0015M sodium citrate and 50% formamide, followed by at least one but not more than two washes in 2x SSC, 0.1% SDS at room temperature for not more than 20 minutes, followed by a wash in 0.1x SSC, 0.1% SDS at 50°C for not more than 10 minutes, or (ii) at 65-68°C in a buffer comprising 0.015M sodium chloride and 0.0015M sodium citrate, followed by at least one but not more than two washes in 2x SSC, 0.1% SDS at room temperature for no more than 20 minutes, followed by a wash in 0.1x SSC, 0.1% SDS at 50°C for no more than 10 minutes, and wherein the encoded polypeptide, when heterodimerized to human $\alpha 2$ polypeptide, is capable of regulating thyroidal function or promoting thyroid differentiation or proliferation. The specification provides further discussion of stringent hybridization conditions (*see, e.g.*, page 31, line 20 through page 33, line 10).

Finally, notes that the Federal Circuit has indicated that “[g]iven the sequence of a single strand of DNA or RNA, it may have become a routine matter to envision the precise sequence of a ‘complementary’ strand that will bind to it,” and therefore, “disclosure of a DNA sequence might support a claim to the complementary molecules that can hybridize to it.” *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 925 (Fed. Cir. 2004). Applicant contends that one of ordinary skill in the art could readily determine the structure of nucleic acid molecules that are complementary to the nucleotide sequences recited in claims 1-3 and would recognize that Applicant was in possession of the claimed invention. Thus, withdrawal of the rejections of record comports with CAFC guidance.

Applicant submits that in view of Federal Circuit precedent and guidance, as well as the disclosed sequences and highly stringent hybridization conditions explicitly disclosed in the instant specification and claims, the rejected claims satisfy the written description requirement of 35 U.S.C. § 112, first paragraph. Accordingly, applicants respectfully request that the rejection of the claims under 35 U.S.C. §112, first paragraph written description, be reconsidered and withdrawn.

VI. Response to the Rejection of Claims 2, 4-5, 7 and 11 Under 35 U.S.C. §102(b) or
Alternatively Under 35 U.S.C. §103(a)

The Patent Office rejected claims 2, 4-5, 7 and 11 under 35 U.S.C. §102(b) as anticipated or alternatively under 35 U.S.C. §103(a) as obvious over Mahairas, Locus AQ495547. Applicants traverse the rejection and submit the following comments.

A cited reference must put the claimed invention in the public domain. (“[T]he reference must describe the applicant's claimed invention sufficiently to have placed a person of ordinary skill in the field of the invention in possession of it.” *In re Spada*, 911 F.2d 705, 708 (Fed. Cir. 1990). As applicants pointed out in the previous response, Mahairas does not meet this threshold. Mahairas is simply a stretch of unannotated and uncharacterized genomic DNA. By contrast, applicants provide a discrete coding sequence with a recited activity. Mahairas presents neither of these.

The Patent Office states, “[c]ontrary to applicants argument that the reference must teach both how to make and use the claimed invention, all that is required for anticipation is that the reference teach how to *make* what is claimed, in a manner that would enable said making.” *Office Action*, page 5-6. The Patent Office cited *In re Schoenwald* in support of its argument, apparently for the proposition that “no utility need be disclosed by the reference.” *Office Action*, page 6. Applicants’ arguments do not focus on the lack of utility of Mahairas--although Mahairas certainly fails this inquiry as well--but instead go to the position that Mahairas is a not an enabling reference, *i.e.*, does not put the claimed invention in the public domain, and therefore the claims were improperly rejected over this reference.

Applicants again submit that a proper anticipatory reference requires that the disclosure enables those of ordinary skill in the art to make *and use* the claimed invention. This position is comports with CAFC guidance: “To anticipate, the reference must also enable one of skill in the art to make *and use* the claimed invention.” *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1374 (Fed. Cir. 2001), citing *In re Donohue*, 766 F.2d 531, 533 (Fed. Cir. 1985) (emphasis added). Mahairas does not teach how to make *and use* the claimed invention and therefore is an improper reference.

Applicants further submit that the Patent Office’s argument that the functional feature recited in the claims is assumed to be inherent in Mahairas is also inconsistent with CAFC precedent. A reference can anticipate if the anticipatory reference *necessarily* contains a particular property of the claimed invention. *Continental Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed Cir. 1991). See also *SKB v Apotex* 403 F.3d 1331, 1343 (Fed. Cir. 2005) (“a prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is *necessarily* present, or inherent, in the single anticipating reference.” emphasis added). The Patent Office has admitted that it is unsure whether the recited functional limitation is found in Mahairas. “The examiner is unable to determine whether the prior art disclosure possesses the unrecited characteristics or property.” *Office Action of 11/21/02*, page 11. Since it is not clear that the cited reference *necessarily* has the functional feature recited in the rejected claims, the cited reference cannot support an anticipation rejection as it does not teach each and every element of the claimed invention either explicitly or inherently.

Moreover, since the cited reference does not disclose each and every element of the claimed invention, it also fails the first prong of the *prima facie* case of obviousness and cannot support a rejection under 35 U.S.C. §103(a).

Applicants again strenuously submit that the rejection under 35 U.S.C. §102(b) or alternatively under 35 U.S.C. §103(a) is inconsistent with C.A.F.C. guidance and that Mahairas cannot support this type of rejection. Applicants respectfully request that the rejection of the claims under 35 U.S.C. §102(b) or alternatively under 35 U.S.C. §103(a) be reconsidered and withdrawn.

VII. Response to the Provisional Double Patenting Rejection

The Patent Office provisionally rejected claims 1-8, 10, 11, 47-51, 61 and 65 over claims 1-8, 10, 11, 47-51, 61 and 65 of copending U.S. Patent Application Serial Number 10/449140 on the grounds of non-statutory obviousness-type double patenting.

Applicants acknowledge the Patent Office's provisional rejection. As no claims have yet been allowed in either the instant application or in U.S. Patent Application Serial Number 10/449140, applicants will address the provisional rejection upon notification of allowable claims in either application.

Response dated November 7, 2006

Reply to Final Rejection dated June 23, 2006

VIII. Conclusions

Applicants submit that the claims are in condition for allowance. Accordingly, applicants respectfully request that the rejections of record be reconsidered and withdrawn, and a Notice of Allowance issued.

If any small matter remains outstanding after the Examiner has reviewed the amendments and remarks presented herein, the Examiner is respectfully requested to telephone the undersigned attorney at the telephone number provided below to resolve any such matter.

Respectfully submitted,



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